Canine atopy is defined as an inherited predisposition to develop type I hypersensitivity to environmental allergens.1 Dogs with atopic dermatitis (AD) usually exhibit pruritus of the face, ears, paws and extremities, and possibly the ventrum.2 A great deal of controversy still exists regarding the presence or absence of primary lesions in dogs with AD. Many veterinary dermatologists still feel that primary lesions are absent while others consider erythema a primary lesion (Figure 1).

Most will agree, however, that the majority of lesions seen in dogs with AD are secondary to pruritus. These lesions include saliva staining, alopecia and excoriations (Figures 2 and 3). As the disease progresses and becomes more severe, the skin becomes hyperpigmented and lichenified (Figure 4). The hair coat also loses its luster and becomes dry.

At the present time primary management of AD includes hyposensitization therapy and immunosuppressive therapy with glucocorticoids and cyclosporine. Adjunctive therapy can include various topical preparations, antihistamines, and supplementation with certain omega-6 and omega-3 polyunsaturated fatty acids (PUFAs) (Figure 5).

**THEORY VERSUS EVIDENCE**

In theory, antiinflammatory and immunomodulating properties of PUFAs should help manage the clinical signs of AD.3–5 Both in vitro and in vivo human and laboratory animal studies have shown that omega-3 PUFAs such as eicosapentaenoic acid (EPA) from marine fish oils and alpha-linolenic acid (ALA) from flaxseed oil are incorporated into the cell membrane phospholipid layers of keratinocytes and various inflammatory cells, replacing some of the arachidonic acid (AA). During an inflammatory reaction, these PUFAs are then released along with AA. They are preferred over AA as the substrate of cyclooxygenase and lipoxygenase enzymes (Figure 6). Eicosanoids such as leukotrienes and prostaglandins synthesized from

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**Lesions in Canine Atopic Dermatitis Include:**

- Saliva staining
- Alopecia
- Excoriations
- Hyperpigmented and lichenified skin
- Lusterless and dry hair coat
omega-3 PUFAs are less potent inducers of inflammation than those synthesized from AA. One example is leukotriene B₅, an EPA product that has only 10% of the inflammatory potential of leukotriene B₄, the AA product. The omega-3 eicosanoids also decrease the inflammatory response by further suppressing the production of leukotriene B₅.

Other studies have demonstrated that omega-6 fatty acids have antiinflammatory effects. Omega-6 fatty acids include dihomogamma-linolenic acid (DGLA), which is synthesized from gamma-linolenic acid and found in higher concentrations in evening primrose oil and borage oil. Lipoxygenase enzymes have a higher affinity for DGLA than AA but DGLA is a poor substrate so it decreases the production of leukotriene B₅. DGLA also produces 15-hydroxyeicosatetraenoic acid, an eicosanoid that blocks further synthesis of leukotriene B₅. Cyclooxygenase also has a higher affinity for 15-hydroxyeicosatetraenoic acid than
AA, which leads to an increase in the formation of the anti-inflammatory prostaglandin, PGE1, inhibiting further AA release from cell membranes.

**MARKETED SUPPLEMENTS**

Because of these human and laboratory animal studies, supplements containing various PUFAs were marketed and then used by practitioners and veterinary dermatologists. Unfortunately, although EFA supplements became very popular in the late 1980s, there was little if any scientific proof that they were truly beneficial in the management of canine AD. Several studies done in the early 1990s reported good to excellent results with fatty acid supplementation but these studies were open, uncontrolled, and nonrandomized.4

In the past, the author has found both topical and systemic sources of omega-6 fatty acids such as vegetable oil along with many of the prepared fatty acid supplements to be useful in restoring luster and decreasing the scale in the hair coat of dogs with AD. However, these supplements were of little help in controlling the pruritus and other clinical signs of AD. Thus, the author began using a regimen of marine fish oil (180 mg EPA/10 lb body weight), which delivered a dose of omega-3 PUFA closer to that successfully used in human atopic disease.5 Anecdotally, this higher dose did appear to be more effective in controlling the pruritus.

**ACVD TASK FORCE**

By 2001, when the American College of Veterinary Dermatology task force on canine atopy published its report, there was a plethora of articles on the use of both omega-3 and omega-6 PUFAs in the management of canine AD. The ACVD task force established a set of guidelines for a well-designed fatty acid study, but most studies and reports did not meet these guidelines. Although these studies showed significant improvement with the various supplements and foods, the results must be interpreted with caution because of inherent sources of bias. Randomized, masked, placebo-controlled studies are needed to evaluate the effects of fatty acid supplementation. A crossover study design in which each dog acts as his own control would be ideal for such studies. This is important since it has been shown in early studies that the addition of either omega-3 or omega-6 PUFAs to the food can improve coat and skin character without decreasing the pruritus associated with allergic dermatitis.5

Most of the randomized, masked, controlled studies reported prior to 2001 investigated the effects of high-dose gamma-linolenic acid (GLA). Although the foods in most of these studies were not standardized, this may...
not be a serious fault because the investigators wanted to
determine the effects of high-dose GLA supplementation
on the clinical signs of AD in a clinical setting: Clinical
patients will of course eat a variety of foods. In these stud-
ies the average amount of GLA given was 13 to 15 mg/kg
together with a small amount of EPA (7.6 mg/kg). The
percentage of dogs that improved (greater than 50%
decrease in pruritus) varied from 10% to 85%.8-12

Three randomized, masked, controlled crossover studies
using high-dose GLA have been reported. Two of these stud-
ies used approximately 13 mg GLA/kg body weight/day. Im-
provement was noted in 17% to 40% of patients.13,14 The
third crossover study used 20 mg GLA/kg body
weight/day.15 In this study the food was standardized in all
dogs. At the end of the study there was a significant reduc-
tion in the dermatitis observed in atopic dogs but no change
in their levels of pruritus. Leukotriene B4 did not significant-
ly change after 8 weeks of GLA supplementation while 15-
hydroxyeicosatetraenoic acid increased significantly.

Only one study examined by the ACVD task force
evaluated high-dose omega-3 fatty acid supplementa-
tion.7 This masked, crossover study compared supple-
mentation with marine fish oil to corn oil supplementa-
tion. Each dog received a combined total of 66 mg EPA
and docosahexaenoic acid (DHA)/kg body weight. Foods
were not standardized, but each dog acted as its own con-
trol. Dogs were randomly given corn oil or EPA/DHA for

6 weeks, followed by a 3-week washout
period, and then were switched to the
other supplement for an additional 6
weeks. A significant decrease in pruri-
tus and self-trauma along with signifi-
cant improvement in coat characteris-
tics was noted in the dogs during
EPA/DHA supplementation as com-
pared to corn oil supplementation.

The ACVD task force concluded that it was still unclear whether PUFA
supplementation should be recom-
mended as part of the overall manage-
ment strategy for dogs with AD. The
optimum dose and/or ratio of omega-6
and omega-3 PUFAs for animals with
AD also remains unknown.

NEW STUDIES

Since the publication of the ACVD
task force report several clinical studies using better
research design have been published on the use of fatty
acids in the management of allergic dermatitis in dogs.

Nesbitt and Colleagues

In 2003, Nesbitt and colleagues published a double-
blind study that evaluated four foods with varying quan-
tities of EPA and DHA and different omega-6 to
omega-3 ratios (Table 1).16 Seventy-two dogs with both
seasonal and nonseasonal pruritus consistent with aller-
gic disease (food allergy was not ruled out in many dogs)
were entered into the study and randomly placed in one
of four groups, each fed one of the foods for 56 days.
Fifty-eight dogs completed the study. All four foods led
to a significant decrease in the overall clinical score,
while all foods but one (food C) led to a significant
decrease in pruritus. Plasma fatty acid levels were exam-
ined at the beginning of the study, and there was no sig-
nificant difference between the groups, although dogs
were fed a variety of foods before the study.

At the end of the study, dogs eating food A had sig-
nificant increases in plasma EPA, DHA, and docos-
apentaenoic acid (DPA) and significant decreases in
linoleic acid (LA), GLA, and AA concentrations com-
pared to day 0. Dogs fed food A also had a significant
increase in plasma LA and DHA concentrations and a
significant decrease in the plasma omega-6 to omega-3
ratio when compared to dogs consuming other foods. Dogs fed foods B and C had significant increases in plasma EPA and DHA concentrations along with significant decreases in AA compared to levels on day 0. Dogs fed food D had a significant increase in only plasma LA. Only the dogs fed food A had a significant decrease in PGE2 levels as compared to baseline and to dogs consuming other foods.

The results of this study demonstrate that any change in dietary PUFA concentration and ratio can potentially cause improvements in the clinical appearance and pruritus of dogs with AD. Improvement did not depend on either the total amount or ratio of omega-6 to omega-3 PUFAs in the food.

**World Congress of Veterinary Dermatology Reports**

Two papers on the use of PUFAs in canine patients with AD were presented at the fifth World Congress of Veterinary Dermatology in 2004. The first was a randomized, masked, controlled study evaluating the effects of a test food on the clinical signs of AD in 28 dogs. This test food provided 240 mg EPA/kg and 25 mg GLA/kg metabolic weight. The dogs were fed either the test food and a placebo capsule (15 dogs) or their usual food and a placebo capsule (13 dogs) for a 10-week period, after which nine of the 13 control dogs were switched to the test food. The 24 dogs fed the test food had a significant decrease in pruritus and erythema over the control dogs. Thirteen owners of the dogs fed the test food felt their dogs were significantly improved while only 4 of the 13 owners of control dogs reported significant improvement. Plasma and cutaneous PUFA levels significantly increased in dogs consuming the test food but these increases did not correlate with the clinical responses. This study suggests that PUFA supplementation is useful in the management of canine AD. Unfortunately, once the dogs were switched to the test food, the study was no longer masked or controlled.

A second study reported at the World Congress examined the efficacy of conjugated linoleic acid and black-currant-seed oil in a masked, controlled study. Atopic dogs (n=24; food trial and insect test negative) were divided into four groups (placebo; black-currant-seed oil; conjugated linoleic acid; black-currant-seed oil and conjugated linoleic acid). Although the black-currant-seed-oil group had the best clinical response and a significant increase in plasma concentration of dihomogamma-linolenic acid, no significant improvement was seen in any group. The results indicated that neither conjugated linoleic acid nor black-currant-seed oil at the doses used can be recommended for the treatment of canine AD.

**Saevik and Colleagues**

A multicenter, randomized, controlled study evaluated the steroid-sparing effects of EPA supplementation in dogs with AD. The inclusion criteria for the study dogs were very strict. The 60 dogs included were fed a standard commercial food. After a 3-week acclimation period, they were randomized into a control group (32 dogs) receiving medium-chain triglycerides or a test group (28 dogs) receiving approximately 0.6 ml of a fatty acid supplement (190 mg LA, 105 mg GLA, 9.9 mg EPA, and 6.6 mg DHA) per 10 kg body weight. All dogs were given prednisolone, with the dose based on the previous day’s pruritus score. The mean daily doses of omega-6 and omega-3 PUFA consumed by the test group were 32 mg/kg and 1.8 mg/kg respectively.

**Table 1: Dietary Fatty Acids and Omega-6 to Omega-3 Ratio**

<table>
<thead>
<tr>
<th>Food</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High dose of EPA and DHA, low ratio</td>
<td>High dose of EPA and DHA, intermediate ratio</td>
<td>Intermediate dose of EPA and DHA, intermediate ratio</td>
<td>Low dose of EPA and DHA, high ratio</td>
</tr>
<tr>
<td>Total omega-6</td>
<td>10.95</td>
<td>29.64</td>
<td>17.74</td>
<td>19.5</td>
</tr>
<tr>
<td>Total omega-3</td>
<td>10.25</td>
<td>10.54</td>
<td>3.08</td>
<td>0.73</td>
</tr>
<tr>
<td>Omega-6 to omega-3 ratio</td>
<td>1:1</td>
<td>3:1</td>
<td>6:1</td>
<td>27:1</td>
</tr>
</tbody>
</table>
Pruritus scores at day 0 and day 41 were not significantly different between groups but both groups had a significant decrease in pruritus from day 0 to day 41. There was no additional significant decrease in pruritus in either group from day 41 to day 83. There was also no significant difference in the use of prednisolone between the two groups during the study, although there was a significant decrease in the test group compared to the placebo group over the last 20 days. By day 83, the mean daily dose of prednisolone was 0.12 mg/kg for the test group and 0.24 mg/kg for the placebo group. Thus, dietary PUFA supplementation may have some steroid-sparing effects in allergic dogs, but supplementation for more than 12 weeks may be necessary.

Mueller and Colleagues
In 2005, Mueller and colleagues published two studies investigating the effects of omega-3 fatty acid supplementation on dogs with AD. The first study examined high-dose omega-3 PUFA supplementation on the clinical signs of AD in dogs.20 In a randomized, masked, controlled manner, 29 atopic dogs were fed a standardized food for 8 weeks before the study. Dogs were then divided into three groups: placebo, EPA/DHA supplement, and flaxseed oil supplement. The dogs on EPA/DHA received 50 to 85 mg EPA/kg body weight and 35 to 55 mg DHA/kg daily. The flaxseed oil group received 200 to 335 mg flaxseed oil/kg daily. At the end of the 10-week test there was a significant decrease in pruritus and clinical score in both supplemented groups compared to their scores at day 0. No significant decrease in clinical signs occurred in the placebo group. The percent improvement was examined for individuals in each group (Table 2). There was no correlation between clinical improvement and total omega-3 or omega-6 PUFA intake or in the dietary omega-6 to omega-3 ratio. Therefore, the concentration of individual fatty acids may be more important than total omega-3 and omega-6 fatty acid concentrations.

The same investigators examined the plasma and cutaneous fatty acid levels of the dogs in the above clinical trial.21 At the end of the 10-week study, the EPA/DHA supplemented group had significant increases in plasma ALA and EPA concentrations and a significant decrease in plasma AA concentration. The flaxseed group also had significant increases in plasma ALA. There was no significant difference in the cutaneous concentrations of any fatty acid or eicosanoid (PGE₂ and LTB₄) measured. Neither was there any significant correlation between clinical improvement and plasma or cutaneous fatty acid levels. These results suggest that the response of dogs with AD to omega-3 fatty acid supplementation may involve a mechanism of action independent of fatty acid and eicosanoid levels in plasma or skin.

Abba and Colleagues
Another study examined the effects of fatty acid supplementation on acute and chronic canine AD. This study was not masked, controlled, or randomized.22 The investigators divided 22 dogs with nonseasonal signs of AD into two groups: a preimmunotherapy group (little or no previous therapy) and a postimmunotherapy group (nonresponsive to previous immunotherapy). All dogs were fed a homemade food formulated by the authors. The dogs were supplemented with 17 mg/kg EPA, 5 mg/kg DHA, and 35 mg/kg GLA. The omega-6 to omega-3 ratio was 5.5 to 1. The clinical results were reported only as percentages with no statistical analysis. At the end of 8 weeks the “pre” group had some improvement in pruritus, lesions, and alopecia while the “post” group had little to no improvement.

Gueck and Colleagues
Gueck and coinvestigators have published several in vitro studies examining the effects of various PUFAs on cultured canine mastocytoma cells (C2 cells). In the first study, LA or ALA was added to the culture medium of the mast cells.23 The fatty acid composition and the activity and release of various mast cell mediators were measured. The cells cultured in ALA had increased levels of omega-3 fatty acids, decreased trypase activity, reduced PGE₂ production, and decreased histamine release when compared to unsupplemented cells. The

<table>
<thead>
<tr>
<th>Percentage improvement</th>
<th>Placebo group</th>
<th>EPA/DHA group</th>
<th>Flaxseed oil group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50%</td>
<td>1/9</td>
<td>5/10</td>
<td>4/10</td>
</tr>
<tr>
<td>100%</td>
<td>0/9</td>
<td>2/10</td>
<td>1/10</td>
</tr>
</tbody>
</table>
cells cultured in LA had increased levels of omega-6 fatty acids, increased tryptase activity, and increased histamine release.

In the second study, EPA or AA was added to the mast cell culture. Cells supplemented with either EPA or AA had increased PGE$_2$ levels and histamine release when compared to unsupplemented cells. However, these levels were significantly lower with EPA supplementation compared to AA supplementation.

The addition of GLA or DHA to cell cultures was also examined. Cells supplemented with GLA had significantly elevated concentrations of GLA and dihomogamma-linolenic acid (DGLA) compared to unsupplemented cells. AA levels did not change. With DHA supplementation there was a significant increase in DHA and EPA levels. Neither addition of DHA nor GLA influenced chymase activity. In contrast, addition of GLA to cells significantly increased tryptase activity compared to DHA-supplemented and unsupplemented cells. Neither addition of GLA nor DHA had an effect on spontaneous histamine release or PGE$_2$ production, although stimulated histamine release was decreased in the presence of GLA and diminished by DHA.

Seidel and Colleagues

The influence of fatty acids on the lipid fatty acid composition of canine C2 mast cells in culture was examined in another study. None of the supplemented fatty acids (LA, GLA, AA, ALA, EPA, and DHA) had any influence on cell growth. The elongated and delta 6-desaturated products of the corresponding fatty acids were significantly elevated; however, the delta 5-desaturated products were not measurable and it was assumed that these cells do not have measurable delta 5-desaturase activity. The fatty acid profile seen with C2 mast cells in culture after the addition of various fatty acids corresponds to that seen in atopic human patients when supplemented with the same fatty acids. Therefore, canine mast cells may have defects in fatty acid metabolism, as do the cells of atopic humans, and may be a good model to study canine atopic disease.

The in vitro studies may shed some light on the mechanism of action of PUFA supplementation in canine allergic dermatitis. The addition of various omega-3 fatty acids and GLA caused a significant decrease in the inflammatory mediators produced by cultured mast cells. Since mast cells are still considered to be important in the pathogenesis of canine AD, it may be more prudent to look at mast cell mediator levels instead of eicosanoid levels when evaluating dogs supplemented with various fatty acids.

CONCLUSION

Newer clinical studies provide additional evidence that omega-3 fatty acid supplementation alone or in combination with GLA does have some clinical benefit in the management of canine allergic dermatitis. The mechanism of action for this clinical benefit remains unclear because none of the studies demonstrated a correlation between changes in plasma or skin fatty acid or eicosanoid levels and clinical improvement. Given the wide dose ranges, the importance of total omega-3 or omega-6 fatty acid concentrations, the concentrations of individual fatty acids, and the optimum omega-6 to omega-3 ratio cannot be determined. The in vitro studies with mast cells give us another way to explore the effects of PUFA on canine atopic dermatitis.

REFERENCES


